General

Guideline Title

Fertility drugs and cancer: a guideline.

Bibliographic Source(s)

Practice Committee of the American Society for Reproductive Medicine. Fertility drugs and cancer: a guideline. Fertil Steril. 2016 Dec;106(7):1617-26. [115 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the level of evidence (Level I-III) and strength of the recommendations (Grade A-C) are given at the end of the "Major Recommendations" field.

Ovarian Cancer

Summary Statements

Based on the available data, the Practice Committee can be reasonably reassured that there is no meaningful increased risk of invasive ovarian cancer following the use of fertility drugs in infertile women. (Grade B)
Based on the available data there is fair evidence that the risk of invasive ovarian cancer is not different with one fertility drug compared with another. (Grade B)
While several studies have shown a small increase in the absolute risk of borderline ovarian tumors after fertility treatments, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors. (Grade C)
It is important to note that any absolute increase in risk is small, and these tumors are indolent and generally have a favorable prognosis. (Grade B)
There is insufficient evidence to recommend against the use of fertility medications to avoid borderline ovarian tumors. (Grade C)

Breast Cancer

Summary Statement

There is fair evidence that fertility drugs are not associated with an increased risk of breast cancer. (Grade B)

Endometrial Cancer

Summary Statement

Overall, there is fair evidence that fertility drugs are not associated with an increased risk of endometrial cancer. (Grade B)

Other Cancers

Summary Statements

Overall, there is fair evidence that fertility drugs are not associated with an increased risk of invasive thyroid cancer. (Grade B)
Overall, there is insufficient evidence that fertility drugs are associated with an increased risk of melanoma. (Grade C)
Overall, there is fair evidence that fertility drugs are not associated with an increased risk of colon cancer. (Grade B)
Based on a single study, there is insufficient evidence that fertility drugs are associated with an increased risk of lymphoma. (Grade C)
Overall, there is fair evidence that fertility drugs are not associated with an increased risk of cervical cancer. (Grade B)

Recommendations

Given the available literature, patients should be counseled that infertile women may be at an increased risk of invasive ovarian, endometrial, and breast cancer; however, use of fertility drugs does not appear to increase this risk.
While several studies have shown a small increase in the absolute risk of borderline ovarian tumors after fertility treatments, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors.
It is important to note that borderline ovarian tumors are indolent and generally have a favorable prognosis, and any absolute increase in risk related to fertility drugs is small. Therefore, there is insufficient evidence to recommend against the use of fertility medications to avoid borderline ovarian tumors.

Definitions

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Systematic reviews, meta-analyses, opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Infertility

Guideline Category

Counseling

Risk Assessment

Clinical Specialty

Internal Medicine

Obstetrics and Gynecology

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the association of fertility drugs and cancer risk

Target Population

Women with infertility undergoing treatment with fertility drugs

Interventions and Practices Considered

1. Use of fertility drugs
2. Counseling infertile women about the risk of cancer with use of fertility drugs

Major Outcomes Considered

- Risk of cancer in women using fertility drugs
- Incidence of cancer in women using fertility drugs

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

This clinical practice guideline was based on a systematic review of the literature. The search was restricted to PubMed MEDLINE citations of human subject research published in the English language from 1966 to December 18, 2015using a combination of the following words or word phrases: breast, cancer risk, cancer risk, cancer, cause, cervical, chorionic gonadotropin, clomid, clomifen, clomifene, clomiphene, clomiphene/adverse effects[MeSH], colon, colonic neoplasms/chemically induced[MeSH], colonic neoplasms/epidemiology[MeSH], colonic neoplasms/etiology[MeSH], drug, drugs, endometri*, endometrial neoplasms/chemically induced[MeSH], endometrial neoplasms/etiology[MeSH], endometrial,endometrioid, endometrium, fertility agents, female/adverse effects[MeSH], fertility, fertilization in vitro/adverse effects[MeSH], follicle stimulating hormone/adverse effects[MeSH], FSH, genotoxic*, genotoxic*, genotoxicity, gonadotrophin, gonadotrophins, gonadotropin, gonadotropins, gonadotropins/adverse effects[MeSH], hCG, hMG, human/adverse effects[MeSH], infertility, IVF, letrozole, LH, luteinizing hormone, mammary, medical treatment, medication, medicine, melanoma, melanoma/chemically induced[MeSH], melanoma/epidemiology[MeSH], melanoma/etiology[MeSH], menotropins/adverse effects [MeSH]. neoplasms [MeSH], neoplasms/chemically induced[MeSH], neoplasms/epidemiology*[MeSH], ovar*, ovarian neoplasms/etiology[MeSH], ovarian neoplasms/chemically induced[MeSH], ovarian stimulation, ovarian, ovary, ovulation induction, ovulation induction/adverse effects[MeSH], thyroid neoplasms/chemically induced[MeSH], thyroid neoplasms/epidemiology[MeSH], thyroid neoplasms/etiology[MeSH], thyroid, treatment, treatments, uter*, uterine cervical neoplasms/chemically induced[MeSH], uterine cervical neoplasms/epidemiology[MeSH], uterine cervical neoplasms/etiology[MeSH], uterine, uterus.

Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with an outcome measure, meta-analyses, and relevant articles from bibliographies of identified articles.

Number of Source Documents

A total of 1,332 studies were identified in an electronic search and from examination of reference lists from primary and review articles, 113 of which were selected for inclusion in this systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Systematic reviews, meta-analyses, opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The quality of the evidence was evaluated using the grading system found in the "Rating Scheme for the Strength of the Evidence" field and is assigned for each reference in the bibliography (see the original guideline document).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The literature was reviewed to answer the following question:

> Are fertility drugs associated with an increased risk of cancer?

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document was reviewed by American Society for Reproductive Medicine members, and their input was considered in the preparation of the final document. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each summary statement supporting the recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The importance of understanding any existing relationship between fertility medications and cancer risk is crucial because the use of these medications has become quite common, with approximately 1 million in vitro fertilization (IVF) cycles reported per year worldwide in addition to an unknown number of ovulation induction cycles.

Potential Harms

Based on available data, there does not appear to be a meaningful increased risk of invasive ovarian cancer, breast cancer, or endometrial cancer following the use of fertility drugs. Several studies have shown a small increased risk of borderline ovarian tumors; however, there is insufficient consistent evidence that a particular fertility drug increases the risk of borderline ovarian tumors, and any absolute risk is small.

Qualifying Statements

Qualifying Statements

- This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations.
- See "Methodological Limitations of Epidemiologic Studies" section in the original guideline document.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Dec

Guideline Developer(s)

American Society for Reproductive Medicine - Nonprofit Organization

Source(s) of Funding

American Society for Reproductive Medicine

Guideline Committee

Practice Committee of the American Society for Reproductive Medicine

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Financial Disclosures/Conflicts of Interest

All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the American Society for Reproductive Medicine Web site .

Availability of Companion Documents

Continuing medical education (CME) credit related to this guideline is available from the American Society for Reproductive Medicine Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on March 27, 2017. The information was verified by the guideline developer on April 17, 2017.

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